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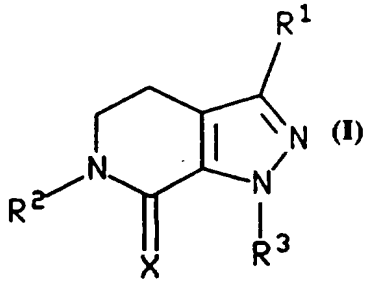
(54) Title: BICYCLIC TETRAHYDRO PYRAZOLOPYRIDINES AND THEIR USE AS MEDICAMENTS

(57) Abstract

Compounds of formula (I) wherein R^1, R^2, R^3 and X are as defined. The compounds of formula (I) and the pharmaceutically acceptable salts thereof are useful in inhibiting phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) and in the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF.



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BICYCLIC TETRAHYDRO PYRAZOLOPYRIDINES AND THEIR USE AS MEDICAMENTS

Background of the Invention

This invention relates to a series of bicyclic tetrahydro pyrazolopyridines which are selective inhibitors of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (hereinafter TNF) and as such are useful in the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases; and AIDS, septic shock and other diseases involving the production of TNF.

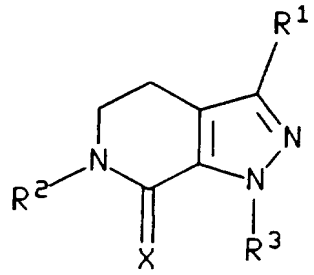
This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans and to pharmaceutical compositions useful therefor.

Since the recognition that cyclic AMP is an intracellular second messenger (E.W. Sutherland, and T. W. Rall, Pharmacol. Rev., 1960, 12, 265), inhibition of the phosphodiesterases has been a target for modulation and, accordingly, therapeutic intervention in a range of disease processes. More recently, distinct classes of PDE have been recognized (J.A. Beavo and D. H. Reifsnyder, TiPS, 1990, 11, 150), and their selective inhibition has led to improved drug therapy (C.D. Nicholson, R. A. Challiss and M. Shahid, TiPS, 1991, 12, 19). More particularly, it has been recognized that inhibition of PDE type IV can lead to inhibition of inflammatory mediator release (M.W. Verghese et al., J. Mol. Cell Cardiol., 1989, 12 (Suppl. II), S 61) and airway smooth muscle relaxation (T. J. Torphy in Directions for New Anti-Asthma Drugs, eds S. R. O'Donnell and C. G. A. Persson, 1988, 37, Birkhauser-Verlag). Thus, compounds that inhibit PDE type IV, but which have poor activity against other PDE types, would inhibit the release of inflammatory mediators and relax airway smooth muscle without causing cardiovascular effects or antiplatelet effects.

TNF is recognized to be involved in many infectious and auto-immune diseases (W. Friers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62, S11).

Summary of the Invention

The present invention relates to compounds of the formula



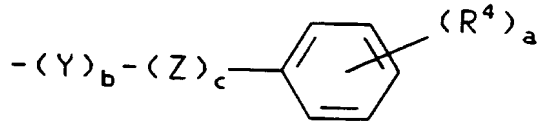
I

and pharmaceutically acceptable salts thereof;

wherein R^1 is hydrogen, (C^1-C^3)alkyl, (C^2-C^3)alkenyl, (C^3-C^5)cycloalkyl or methylene (C^3-C^5)cycloalkyl wherein each alkyl or alkenyl group may be optionally substituted with up to two (C^1-C^2)alkyl or trifluoromethyl groups or up to three halogens;

X is oxygen or two hydrogen atoms;

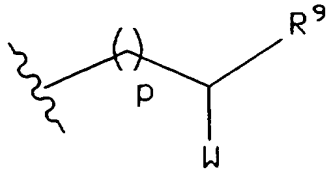
R^2 and R^3 are each independently selected from the group consisting of hydrogen; (C^1-C^{14})alkyl optionally substituted with halogen or cyano; (C^1-C^{14})alkyl sulfonyl; (C^1-C^{14})alkoxy; naphthalyl; (C^2-C^7)alkenyl; (C^3-C^7)cycloalkyl; (C^1-C^4)alkyl(C^3-C^7)cycloalkyl; (C^3-C^7)cycloalkyl(C^1-C^4)alkyl; (C^4-C^7)heterocyclic group containing oxygen; sulphur; SO_2 or NR^5 wherein R^5 is hydrogen or (C^1-C^4)alkyl; (C^4-C^7)heterocycloalkyl-$(W)_d$ wherein the (C^4-C^7)heterocycloalkyl group contains one or more oxygen; sulphur; SO_2 or NR^5 groups wherein R^5 is hydrogen or (C^1-C^4)alkyl optionally substituted with halogen or (C^1-C^4)alkyl, d is 0 or 1 and W is (C^1-C^4)alkyl, CO or sulfonyl; $CONR^{10}R^{11}$ wherein R^{10} and R^{11} are each independently hydrogen or (C^1-C^4)alkyl; (C^1-C^5)alkyl carbonyl; (C^1-C^5)alkoxy carbonyl; (C^1-C^5)alkyl carbonyl (C^1-C^5)alkyl; (C^1-C^5)alkoxy carbonyl (C^1-C^5)alkyl; (C^1-C^5)alkoxy(C^1-C^5)alkyl; $R^{12}R^{13}N$(C^1-C^5)alkyl wherein R^{12} and R^{13} are each independently hydrogen or (C^1-C^5)alkyl; or a group of the formula



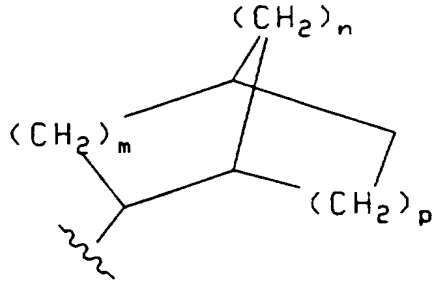
II

wherein a is an integer from 0 to 5; b and c is O or 1; R^4 is independently selected from hydrogen, hydroxy, (C^1-C^5)alkyl, (C^2-C^5)alkenyl, (C^1-C^5)alkoxy, (C^3-C^6)cycloalkoxy,

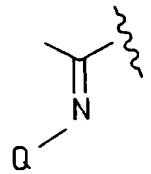
halogen, trifluoromethyl, CO_2R^6, $CONR^6R^7$, NR^6R^7, CONHOH, CN, NO_2 or $SO_2NR^6R^7$ wherein R^6 and R^7 are each independently hydrogen or (C^1-C^4)alkyl; wherein Y is (C^1-C^4)alkyl, (C^2-C^5)alkylene or (C^2-C^6)alkenyl optionally substituted with up to two (C^1-C^7)alkyl or (C^3-C^7)cycloalkyl groups; and Z is oxygen, sulphur, CO, SO_2 or NR^8 wherein R^8 is hydrogen or (C^1-C^4)alkyl; or a group of the formula



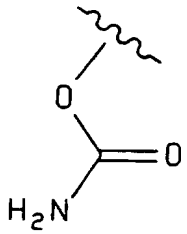
wherein p is an integer from 1 to 3, W is hydroxy, R^9 is (C^1-C^3)alkyl; wherein each said alkyl, alkenyl, cycloalkyl, alkoxyalkyl or heterocyclic group may be optionally substituted with one to fourteen, preferably one to five, of the group consisting of (C^1-C^2)alkyl, trifluoromethyl or halogen; or the group of the formula



wherein m, n and p are 1 or 2; or a group of the formula

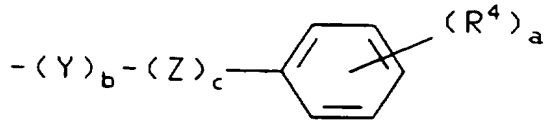


wherein Q is hydroxy or a group of the formula



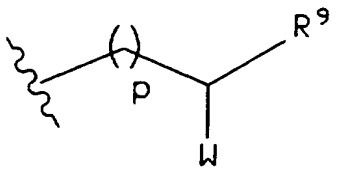
with the proviso that when R^1 is ethyl and R^2 is 4-methylphenyl, R^3 cannot be hydrogen, methyl, phenyl, 4-fluorophenyl or 2-pyridyl and with the proviso that when R^2 is 4-methylphenyl and R^3 is 4-fluorophenyl, R^1 cannot be phenyl, methyl or n-propyl and with the proviso that when R^1 is ethyl and R^2 is phenyl, R^3 cannot be 4-chlorophenyl, 4-fluorophenyl or 4-methylphenyl, with the proviso that when R^1 is ethyl and R^2 is 4-methoxyphenyl, R^3 cannot be 4-fluorophenyl and with the proviso that when W is CO or sulfonyl, d is 1;

with the proviso that R^2 and R^3 cannot both be independently selected from the group consisting of hydrogen, (C^1-C^{14})alkyl, (C^1-C^{14})alkoxy, (C^2-C^7)alkenyl, (C^4-C^7)heterocyclic group containing oxygen, sulphur, SO_2 or NR^5 wherein R^5 is hydrogen or (C^1-C^4)alkyl, or a group of the formula



II

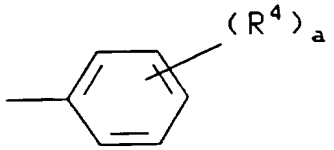
wherein a is an integer from 1 to 5; b and c is O or 1; R^4 is hydrogen, hydroxy, (C^1-C^5)alkyl, (C^2-C^5)alkenyl, (C^1-C^5)alkoxy, (C^3-C^6)cycloalkoxy, halogen, trifluoromethyl, CO_2R^6, $CONR^6R^7$, NR^6R^7, NO_2 or $SO_2NR^6R^7$ wherein R^6 and R^7 are each independently hydrogen or (C^1-C^4)alkyl; wherein Z is oxygen, sulphur, SO_2 or NR^8 wherein R^8 is hydrogen or (C^1-C^4)alkyl; and Y is (C^1-C^5)alkylene or (C^2-C^6)alkenyl optionally substituted with up to two (C^1-C^7)alkyl or (C^3-C^7)cycloalkyl groups; or a group of the formula



wherein p is an integer from 1 to 3, W is oxo or hydroxy, R^9 is $(C^1\text{-}C^3)$alkyl; wherein each said alkyl, alkenyl, cycloalkyl, alkoxyalkyl or heterocyclic group may be optionally substituted with one to fourteen, preferably one to five, of the group consisting of $(C^1\text{-}C^2)$alkyl, trifluoromethyl or halogen.

The above proviso is added to exclude subject matter in prior filed PCT Patent Application No. PCT/IB/94/00156.

In one embodiment, the invention relates to a compound of formula I wherein R^1 is $(C^1\text{-}C^3)$alkyl and R^3 is $(C^3\text{-}C^7)$cycloalkyl, $(C^4\text{-}C^7)$heterocyclic group containing SO_2 or a group of the formula



III

wherein a is an integer from 1 to 5 and R^4 is independently selected from hydrogen, hydroxy, $(C^1\text{-}C^5)$alkyl, $(C^1\text{-}C^5)$alkoxy or halogen.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is ethyl or isopropyl; R^2 is phenyl, 2-methylphenyl, 3-methylphenyl, 2-methoxyphenyl,3-methoxyphenyl,2-hydroxy-phenyl,3-hydroxyphenyl,4-hydroxyphenyl, cyclopropylmethyl, benzyl, isobutyl, isobutenyl, 2-ethylphenyl, naphthalenyl, 2-chlorophenyl, 3-methylbutyl, dimethylcarbamyl, 1-methylbenzyl, isopropyl, 1-picolyl, 2-picolyl, 3-picolyl, 2-methyl-5-chlorophenyl, 2-chlorothiophen-5-ylmethyl, 2-hydroxy-5-methylphenyl, 3,5-dimethyl-isoxazol-4-ylmethyl, 3-chlorobenzyl, thiophen-2-ylmethyl, 2-hydroxy-5-chlorophenyl, thiophene-2-carbonyl, tetrahydrofurfuryl, 3-cyanobenzyl, morpholine-4-carbonyl, isopropylsulfonyl, 4-methoxyphenylsulfonyl or 3-trifluoromethylphenyl, and R^3 is cyclobutyl, cyclopentyl, cyclohexyl, 3-sulfolanyl, 4-fluorophenyl or 3,4-dichlorophenyl.

The present invention further relates to a pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) and for the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising a pharmaceutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

The present invention further relates to a method for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) comprising administering to a patient an effective amount of a compound according to formula I and the pharmaceutically acceptable salts thereof.

The present invention further relates to a method of treating an inflammatory condition in mammals which comprises administering to said mammal an antiinflammatory amount of a compound of the formula I and the pharmaceutically acceptable salts thereof.

This invention further relates to a method of treating or preventing a condition selected from the group consisting of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising administering to a patient an effective amount of a compound according to formula I and the pharmaceutically acceptable salts thereof.

Detailed Description of the Invention

The term "halogen", as used herein, unless otherwise indicated, includes chloro, fluoro and bromo.

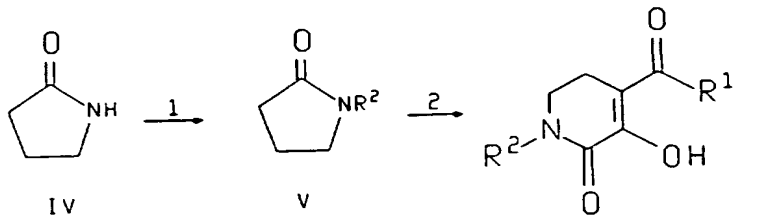
Unless indicated otherwise, the alkyl, alkoxy and alkenyl groups referred to herein may be straight chained or if comprising three or more carbons may be straight chained, branched, cyclic or a combination of cyclic and branched or straight chained moieties.

The "inflammatory diseases" which can be treated according to this invention include, but are not limited to asthma, chronic obstructive pulmonary disease, bronchitis and arthritis.

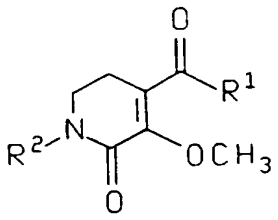
R^1, R^2 and R^3, as used herein, unless otherwise indicated, are as defined above with reference to formula I.

The following reaction schemes illustrate, but are not limiting to the preparation of the compounds of the present invention.

SCHEME 1

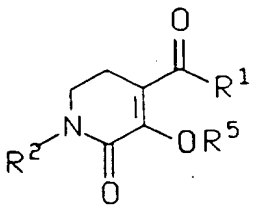


IV V VI

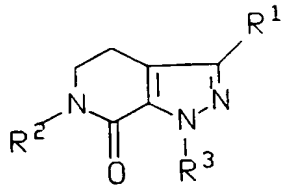


VII

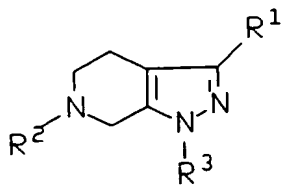
SCHEME 2



VIII



IX



X

In Reaction 1 of Scheme 1, the 2-pyrrolidinone compound of formula IV is converted to the corresponding N-(aryl)-2-pyrrolidone compound V wherein "aryl" is a group of the formula II by reacting IV with an aryl halide neat in the presence of copper power and potassium carbonate. Suitable aryl halides include 1-iodo- or 1-bromo- 4-methoxybenzene, 3-methoxybenzene, 2-methoxybenzene, 3-methylbenzene, 4-methylbenzene, 2-methylbenzene, 3-trifluoromethylbenzene, 2-trifluoromethylbenzene, 3,4-dimethoxybenzene or 3-cyclopentoxy-4-methoxybenzene. The reaction temperature will generally be in the range of about 110°C to about 170°C, preferably about 150°C, for a time period of about 14 hours to about 22 hours, preferably about 18 hours, under inert reaction conditions.

In Reaction 2 of Scheme 1, R^1 halide is added to a suspension of magnesium in an anhydrous aprotic solvent. The reaction mixture is heated to reflux until all the magnesium is consumed and thereafter cooled to a temperature between about -15°C to about 15°C, preferably about 0°C. The N-(aryl)-2-pyrrolidone compound of formula V is then added and the reaction mixture is warmed to room temperature while being stirred for a time period between about 1.5 hours to about 2.5 hours, preferably about 2 hours. Suitable alkyl halides include bromomethane, bromoethane or bromopropane. The preferred anhydrous aprotic solvent is anhydrous ether. Upon completion of the reaction, the desired intermediate may be isolated in a conventional manner, e.g., by first washing the combined organics with water and brine, then drying over sodium sulfate, filtering and concentrating under reduced pressure to afford a readily-recoverable precipitate in the form of a white solid.

The above precipitate is converted to the corresponding 1,2,5,6-tetrahydropyridine compound of formula VI by dispersing the precipitate in a mixture of a non-polar aprotic solvent and base. Upon vigorous stirring, ethyl oxalyl chloride is added and the reaction mixture is heated to reflux for a time period between about 1.5 hours to about 4.5 hours, preferably about 3.0 hours. The preferred non-polar aprotic solvent is benzene and the preferred base is sodium hydroxide. The solvents are removed and the resulting residue is treated with a solution of sodium alkoxide in ethanol. After heating at reflux for a time period between about 1 hour and about 3 hours, preferably about 1.5 hours, the mixture is concentrated under reduced pressure and acidified to pH=3 with hydrochloric acid.

In Reaction 3 of Scheme 1, the compound of formula VI is converted to the corresponding 3-methoxy-1,2,5,6-tetrahydropyridine compound VII by heating to reflux a reaction mixture of VI and 3-methyl-1-p-tolyltriazene in an aprotic solvent. The preferred aprotic solvent is 1,2-dichloroethane. The time period for the reaction is between about 30 minutes to about 120 minutes, preferably about 45 minutes.

In Reaction 1 of Scheme 2, the 1,2,5,6-tetrahydropyridine compound of formula VIII, wherein R^5 is hydrogen or methyl, is converted to the corresponding 4,5,6,7-tetrahydro-7-oxo-1H-pyrazolo[3,4-c]pyridine compound IX by reacting VIII with a hydrazine of the formula R^3HNNH_2. Both derivatives of the compound of formula VIII, 3-hydroxy and 3-methoxy, may be used as starting materials under one of three different sets of reaction conditions.

Under one set of reaction conditions, the 1,2,5,6-tetrahydropyridine compound of formula VIII is converted to the corresponding compound of formula IX by reacting VIII with a hydrazine hydrochloride and sodium alkoxide in an anhydrous polar protic solvent. The preferred sodium alkoxide is sodium methoxide and the preferred anhydrous polar protic solvent is anhydrous ethanol. The reaction mixture is heated to reflux for a time period between about 9 hours to about 15 hours, preferably about 12 hours.

Under a second set of reaction conditions, the 1,2,5,6-tetrahydro-pyridine compound VIII is converted to the corresponding compound of formula IX by reacting VIII with hydrazinobenzoic acid in an anhydrous polar protic solvent, preferably ethanol. The reaction mixture is heated to reflux for a time period between about 16 hours to about 24 hours, preferably about 20 hours. The compound IX so formed may be further reacted to give the corresponding 1-(4-benzamide)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine compound by reacting IX with sodium methoxide in a polar protic solvent, preferably methanol, for a time period between about 15 minutes to about 45 minutes, preferably 30 minutes. The polar protic solvent is removed under reduced pressure, the solid residue is suspended in a non-polar aprotic solvent, perferably benzene, and thereafter, the non-polar solvent is removed under reduced pressure. The resulting dry solid is suspended in cold ether and treated with oxalyl chloride and N,N-dimethylformamide and allowed to stir for a time period between about 30 minutes to about 90 minutes, preferably 60 minutes. The solvent is then removed and the crude residue is dissolved in dry tetrahydrofuran. The resulting

solution is added dropwise to stirred ammonium hydroxide at a temperature between about -10°C to about 10°C, preferably 0°C.

Under a third set of reaction conditions, the 1,2,5,6-tetrahydropyridine compound of formula **VIII** is converted to the corresponding compound of formula **IX** by reacting **VIII** with a hydrazine hydrochloride in a polar protic solvent, preferably methanol. The reaction mixture is heated to a temperature between about 70°C to about 110°C, preferably about 90°C, under a gentle stream of nitrogen until all of the solvent is removed. The neat mixture is then heated to a temperature between about 120°C to about 180°C, preferably about 150°C, for a time period between about 30 minutes to about 90 minutes, preferably 60 minutes.

The compounds so formed of formula **IX** may be converted to the corresponding 6-R^2-4,5,6,7-tetrahydro-7-oxo-1H-pyrazolo [3,4-c]pyridine compound, wherein R^2 is other than the group of formula **II**, by reacting a solution of **IX** in a polar aprotic solvent, preferably acetonitrile, with a solution of ammonium cerium (IV) nitrate in water at a temperature between about -15°C to about 15°C, preferably about 0°C, for a time period between about 20 minutes to about 50 minutes, preferably about 35 minutes. Upon completion of the reaction, the mixture is diluted with water and extracted with ethyl acetate. The combined organics are then washed with saturated sodium bicarbonate followed by sodium sulfite. The compound so formed in a polar aprotic solvent, preferably tetrahydrofuran, is treated with sodium hydride, heated to reflux and stirred for a time period between about 30 minutes to about 60 minutes, preferably 45 minutes. The reaction mixture is cooled to a temperature between about 20°C to about 30°C, preferably about 25°C, and an alkyl halide of formula R^2 halide, wherein R^2 is as defined with reference to formula I other than a group of formula II, is added. The reaction mixture is stirred and heated to reflux for a time period between about 12 hours to about 20 hours, preferably 16 hours.

In Reaction 2 of Scheme 2, the 2-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine compound **IX** is converted to the corresponding compound of formula **X** by reacting **IX** with a reducing agent, preferably lithium aluminum hydride, in a non-polar aprotic solvent, preferably ether. The reaction is stirred for a time period between about 12 hours to about 20 hours, preferably 16 hours. Water and base, preferably sodium hydroxide, is then added and the reaction mixture is stirred for a time period between

about 1.5 hours to about 2.5 hours, preferably 2 hours, and filtered. The filtrate is concentrated to a white solid.

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit phosphodiesterase IV (PDE_4) and, consequently, demonstrate their effectiveness for treating inflammatory diseases is shown by the following in vitro assay.

BIOLOGICAL ASSAY

(Human lung PDE_{IV})

Thirty to forty grams of human lung tissue is placed in 50 ml of pH 7.4 Tris/phenylmethylsulfonyl fluoride (PMSF)/sucrose buffer and homogenized using a Tekmar Tissumizer® (Tekmar Co., 7143 Kemper Road, Cincinnati, Ohio 45249) at full speed for 30 seconds. The homogenate is centrifuged at 48,000 x g for 70 minutes at 4°C. The supernatant is filtered twice through a 0.22 μm filter and applied to a Mono-Q FPLC column (Pharmacia LKB Biotechnology, 800 Centennial Avenue, Piscataway, New Jersey 08854) pre-equilibrated with pH 7.4 Tris/PMSF buffer. A flow rate of 1 ml/minute is used to apply the sample to the column, followed by a 2 ml/minute flow rate for subsequent washing and elution. Sample is eluted using an increasing, step-wise NaCl gradient in the pH 7.4 Tris/PMSF buffer. Eight ml fractions are collected. Fractions are assayed for specific PDE_{IV} activity, determined by [^{3}H]cAMP hydrolysis and the ability of a known PDE_{IV} inhibitor (e.g. rolipram) to inhibit that hydrolysis. Appropriate fractions are pooled, diluted with ethylene glycol (2 ml ethylene glycol/5 ml of enzyme prep) and stored at -20°C until use.

Compounds are dissolved in DMSO at a concentration of 10 mM and diluted 1:25 in water (400 μM compound, 4% DMSO). Further serial dilutions are made in 4% DMSO to achieve desired concentrations. Final DMSO concentration in assay tube is 1%. In duplicate the following are added, in order, to a 12 x 75 mm glass tube (all concentrations are given as final concentrations in assay tube).

i) 25 μl compound or DMSO (1%, for control and blank)

ii) 25 μl pH 7.5 Tris buffer

iii) [^{3}H]cAMP (1 μM)

iv) 25 μl PDE_{IV} enzyme (for blank, enzyme is preincubated in boiling water for 5 minutes)

The reaction tubes are shaken and placed in a water bath (37°C) for 20 minutes, at which time the reaction is stopped by placing the tubes in a boiling water

bath for 4 minutes. Washing buffer (0.5 ml, 0.1M 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (HEPES)/0.1M NaCl, pH 8.5) is added to each tube on an ice bath. The contents of each tube are applied to an Affi-Gel 601 column (Biorad Laboratories, P.O. Box 1229, 85A Marcus Drive, Melville, New York 11747) (boronate affinity gel, 1 ml bed volume) previously equilibrated with washing buffer. [^{3}H]cAMP is washed with 2 x 6 ml washing buffer, and [^{3}H]5'AMP is then eluted with 4 ml of 0.25M acetic acid. After vortexing, 1 ml of the elution is added to 3 ml scintillation fluid in a suitable vial, vortexed and counted for [^{3}H].

$$\% \text{ inhibition} = 1 - \frac{\text{average cpm (test compound) - average cpm (blank)}}{\text{average cpm (control) - average cpm (blank)}}$$

IC_{50} is defined as that concentration of compound which inhibits 50% of specific hydrolysis of [^{3}H]cAMP to [^{3}H]5'AMP.

(TNF)

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Peripheral blood (100 mls) from human volunteers is collected in ethylenediaminetetraacetic acid (EDTA). Mononuclear cells are isolated by Ficoll/Hypaque and washed three times in incomplete HBSS. Cells are resuspended in a final concentration of 1 x 10^6 cells per ml in pre-warmed RPMI (containing 5% FCS, glutamine, pen/step and nystatin). Monocytes are plated as 1 x 10^6 cells in 1.0 ml in 24-well plates. The cells are incubated at 37°C (5% carbon dioxide) and allowed to adhere to the plates for 2 hours, after which time non-adherent cells are removed by gentle washing. Test compounds (10μl) are then added to the cells at 3-4 concentrations each and incubated for 1 hour. LPS (10μl) is added to appropriate wells. Plates are incubated overnight (18 hrs) at 37°C. At the end of the incubation period TNF was analyzed by a sandwich ELISA (R&D Quantikine Kit). IC_{50} determinations are made for each compound based on linear regression analysis.

Pharmaceutically-acceptable acid addition salts of the compounds of this invention include, but are not limited to, those formed with HCl, HBr, HNO_3, H_2SO_4, H_3PO_4, CH_3SO_3H, p-$CH_3C_6H_4SO_3H$, CH_3CO_2H, gluconic acid, tartaric acid, maleic acid and succinic acid. Pharmaceutically-acceptable cationic salts of the compounds of this

invention of formula I wherein R^4 is CO_2R^6 and R^6 is hydrogen include, but are not limited to, those of sodium, potassium, calcium, magnesium, ammonium, N,N'-dibenzylethylenediamine, N-methylglucamine (meglumine), ethanolamine and diethanolamine.

For administration to humans in the curative or prophylactic treatment of inflammatory diseases, oral dosages of the compounds of formula I and the pharmaceutically acceptable salts thereof (hereinafter also referred to as the active compounds of the present invention) are generally in the range of from 0.1-100 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.1 to 50 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration are typically within the range of 0.1 to 10 mg per single dose as required. For intranasal or inhaler administration, the dosage is generally formulated as a 0.1 to 1% (w/v) solution. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and all such dosages are within the scope of this invention.

For administration to humans for the inhibition of TNF, a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

For human use, the active compounds of the present invention can be administered alone, but will generally be administered in an admixture with a pharmaceutical diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovales either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. They may be injected parenterally; for example, intravenously, intramuscularly or subcutaneously.

For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances; for example, enough salts or glucose to make the solution isotonic.

Thus in a further aspect the invention provides pharmaceutical compositions comprising a compound of the formula I and the pharmaceutically acceptable salts thereof together with a pharmaceutically acceptable diluent or carrier.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

Example 1

1-Cyclohexyl-3-ethyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A solution of 3-methoxy-1-(3-methoxyphenyl)-2-oxo-4-propionyl-1,2,5,6-pyridine (0.80 grams, 2.8 mmole) and cyclohexylhydrazine hydrochloride (0.54 grams, 3.6 mmole) in methanol (15 ml) was warmed to 90°C under a gentle stream of nitrogen until all of the solvent was removed. The neat mixture was then heated to approximately 150°C under nitrogen for 1 hour. After cooling to room temperature, the mixture was dissolved in ether and washed with 1N hydrochloric acid followed by brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Chromatography on silica gel using 1:1 ethyl acetate/hexane as eluent gives 0.47 grams of the title compound as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) 1.20-1.52 (m, 6H, including t at 1.23, J = 7.6 Hz, 3H), 1.64-1.74 (m, 1H), 1.80-2.06 (m, 6H), 2.67 (q, J = 7.6 Hz, 2H), 2.87 (t, J = 6.7 Hz, 2H), 3.82 (s, 3H), 3.97 (t, J = 6.7 Hz, 2H), 5.13 (tt, J = 4.3 and 11.3 Hz, 1H), 6.79-6.93 (m, 3H), 7.31 (t, J = 8.1 Hz, 1H); HRMS calculated for $C_{21}H_{27}N_3O_2[M^+]$: 353.2103. Found: 353.2094.

Examples 2-16

Reaction of the appropriate hydrazine hydrochloride with the requisite 4-alkanoyl-3-methoxy-2-oxo-1,2,5,6-tetrahydropyridine, analogous to the procedure of Example 1, affords the following compounds of formula IX.

Ex.#	R^1	R^2	R^3	M.p.°C	Mass Spectra or Analysis (calcd.) %C, %H, %N	Mass Spectra or Analysis (found) %C, %H, %N
2	ethyl	2-methoxy-phenyl	cyclobutyl	123-4	70.13, 7.12, 12.91	69.93, 7.09, 12.81
3	ethyl	2-methyl-phenyl	3-methyl cyclo-pentyl	oil	[M+] 337.46	MS (m/z) 338
4	ethyl	2-ethyl-phenyl	cyclobutyl	oil	[M+] 323.44	MS (m/z) 324
5	ethyl	2-ethyl-phenyl	cyclo-pentyl	106-7	[M+] 337.46	MS (m/z) 337
6	ethyl	1-naphth-alene	cyclo-pentyl	188-90	[M+] 359.47	MS (m/z) 360
7	ethyl	1-naphth-alene	cyclohexyl	199-201	[M+] 373.5	MS (m/z) 372
8	ethyl	2-chloro-phenyl	cyclo-pentyl	100-3	66.37, 6.45, 12.22	66.65, 6.61, 11.92
9	ethyl	2-chloro-phenyl	cyclohexyl	oil	[M+] 357.88	MS (m/z) 358
10	ethyl	2-methyl-phenyl	bicyclo[2.2.1]hept-2-yl	141-2	75.61, 7.79, 12.02	75.74, 7.84, 11.85
11	ethyl	2-methoxy-5-methyl-phenyl	cyclo-pentyl	94-6	71.36, 7.70, 11.89	71.88, 7.71, 11.43
12	ethyl	5-chloro-2-methyl-phenyl	cyclo-pentyl	109-11	67.12, 6.76, 11.74	67.30, 7.02, 11.21
13	ethyl	5-chloro-2-methyl-phenyl	4-fluoro-phenyl	90-2	[M+] 383.85	MS (m/z) 384
14	ethyl	5-chloro-2-methyl-phenyl	cyclobutyl	135-7	66.37, 6.45, 12.22	67.17, 6.81, 11.78
15	ethyl	5-chloro-2-methoxy-phenyl	4-fluoro-phenyl	129-30	63.08, 4.79, 10.51	63.08, 4.86, 10.41
16	ethyl	2-chloro-phenyl	4-tetra-hydro-pyranyl	oil	[M+] 359.85	MS (m/z) 360

Recrystallization solvents: [a]Ethyl acetate/pentane. [b]Ethyl ether/pentane. [c]Isopropyl ether/pentane. [d]Ethyl/acetate/petroleum ether. [e]Ethyl acetate. [f]Ethyl acetate/hexane.

Example 17

3-Ethyl-6-(4-fluorophenyl)-1-(4-methoxyphenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

To a stirred solution of 3-Ethyl-6-(4-fluorophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (0.3 grams, 0.82 mmole) in 50 ml ether was added lithium aluminum hydride (33 mg, 0.86 mmole). After stirring for 16 hours water (0.5 ml) was added followed by 3N sodium hydroxide (1 ml). After stirring for 2 hours the white precipitate was filtered through celite and the filtrate is concentrated under reduced pressure. Chromatography on a silica gel column using 1:3 ethyl acetate/hexane as eluent gives 0.12 grams of the title compound as a pale yellow paste. ^{1}H NMR (250 MHz, $CDCl_3$) 1.28 (t,J = 7.6 Hz, 3H), 2.66 (q,J = 7.6 Hz, 2H), 2.71 (t,J = 5.7 Hz, 2H), 3.49 (t,J = 5.7 Hz, 2H), 3.84 (s, 3H), 4.23 (s, 2H), 6.84-6.99 (m, 6H), 7.36 (d,J = 9.0 Hz, 2H); MS m/z [M^+] 352.

Examples 18

Reaction of the appropriate 7-oxo-2,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine with lithium aluminum hydride, analogous to the procedure of Example 17, affords the following compounds of formula IX.

Ex.#	R^1	R^2	R^3	M.p.°C	Mol. Weight	Mass Spectra [M^+] (found)
18	ethyl	isobutyl	cyclopentyl	oil	275.44	MS (m/z) 276

Example 19

1-Cyclopentyl-3-ethyl-6-benzyl-7-oxo-4,5,6,7-tetrahydro-1H--pyrazolo[3,4-c]pyridine

A solution of 1-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4,c]pyridine (0.12 grams, 0.51 mmoles) in DMF (5 ml) is treated with 60% sodium hydride in mineral oil (32 mgrams, 0.77 mmoles). After stirring at ambient temperature over 1 hour benzylbromide (0.22 grams, 1.29 mmoles) is added. After 4 hours the mixture is diluted with water (50 ml) and extracted with ethyl acetate. The combined organic layers are washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Chromatography on silica gel eluting with

1:4 ethyl acetate/hexane gives 0.13 grams of the title compound as a colorless oil. MS m/z [M+] 324.

Examples 20-68

Reaction of 1-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine with sodium hydride in DMF followed by addition of the requisite electrophile analogous to the procedure of Example 19, affords the following compounds of formula IX where R^1=ethyl and R^3=cyclopentyl.

Ex. #	electrophile	R^2	Mp°C	Mass Spectra or Analysis (Calcd) %C, %H, %N	Mass Spectra/Analysis (found) %C, %H, %N
20	cyclopropyl methyl bromide	cyclopropyl methyl	oil	[M+] 287.41	MS (m/z) 288
21	cyclopentyl bromide	cyclopentyl	oil	[M+] 301.43	MS (m/z) 302
22	isobutyl bromide	isobutyl	oil	[M+] 289.42	MS (m/z) 290
23	methallyl bromide	methallyl	oil	[M+] 287.41	MS (m/z) 288
24	isoamyl-bromide	3-methyl butyl	oil	[M+] 303.45	MS (m/z) 304
25	ethyl 2-bromo-butyrate	1-ethoxy-carbonyl propyl	oil	[M+] 347.46	MS (m/z) 348
26	dimethyl-carbamyl	dimethyl-carbamyl	oil	[M+] 304.39	MS (m/z) 305
27	neopentyl bromide	neopentyl	oil	[M+] 303.45	MS (m/z) 304
28	ethyl 4-bromo-butyrate	3-ethoxy-carbonyl-propyl	oil	[M+] 347.46	MS (m/z) 348
29	1-bromo-2-phenyl ethane	2-phenyl ethyl	oil	[M+] 337.47	MS (m/z) 338
30	1-bromo-1-phenyl ethane	1-phenyl ethyl	70-1	74.74, 8.06, 12.45	74.66, 8.22, 12.47

Ex. #	electrophile	R^2	Mp°C	Mass Spectra or Analysis (Calcd) %C, %H, %N	Mass Spectra/Analysis (found) %C, %H, %N
31	N,N-dimethyl methylene ammonium chloride	N,N-dimethyl amino methyl	oil	[M+] 290.41	MS (m/z) 291
32	isopropyl bromide	isopropyl	oil	[M+] 275.40	MS (m/z) 276
33	acetyl-chloride	acetyl	oil	[M+] 275.35	MS (m/z) 276
34	2-bromo-methyl-1,3-dioxolane	1,3-dioxolan-2-yl-methyl	52-3	[M+] 319.41	MS (m/z) 320
35	3-picolyl chloride	3-picolyl	oil	[M+] 324.43	MS (m/z) 325
36	2-picolyl chloride	2-picolyl	oil	[M+] 324.43	MS (m/z) 325
37	4-picolyl chloride	4-picolyl	oil	[M+] 324.43	MS (m/z) 325
38	benzene-sulfonyl chloride	benzene-sulfonyl	oil	[M+] 373.48	MS (m/z) 374
39	isopropyl sulfonyl chloride	isopropyl sulfonyl	117-9	56.61, 7.42, 12.38	56.78, 7.43, 12.33
40	2-chloro-5-(chloro-methyl) thiophene	2-chloro-thiophen-5ylmethyl	oil	[M+] 363.91	MS (m/z) 364
41	3-chloro-methyl anisole	3-methoxy benzyl	oil	[M+] 353.47	MS (m/z) 354
42	4-chloro methyl-3,5-dimethyl-isoxazole	3,5-dimethyl-isoxazol-4-ylmethyl	98-9	66.64, 7.65, 16.36	66.46, 7.79, 16.33
43	3-chloro-benzyl bromide	3-chloro-benzyl	oil	[M+] 357.89	MS (m/z) 358

Ex. #	electrophile	R^2	Mp°C	Mass Spectra or Analysis (Calcd) %C, %H, %N	Mass Spectra/Analysis (found) %C, %H, %N
44	2-chloro-benzyl bromide	2-chloro-benzyl	68-9	67.12, 6.76, 11.74	67.13, 7.03, 11.90
45	thiophene-2-sulfonyl chloride	thiophene-2-sulfonyl	oil	[M+] 379.50	MS (m/z) 380
46	4-chloro-benzene sulfonyl chloride	4-chloro-benzene sulfonyl	oil	[M+] 407.92	MS (m/z) 408
47	methane-sulfonyl chloride	methane sulfonyl	55-60	[M+] 311.40	MS (m/z) 312
48	4-methoxy benzene sulfonyl chloride	4-methoxy benzene sulfonyl	118-126	[M+] 403.50	MS (m/z) 404
49	3-chloro-benzene sulfonyl chloride	3-chloro-benzene sulfonyl	89-94	[M+] 407.92	MS (m/z) 408
50	2-chloro-methyl thiophene	thiophen-2-ylmethyl	oil	[M+] 329.47	MS (m/z) 330
51	2,5-dichloro-benzene sulfonyl chloride	2,5-dichloro benzene sulfonyl	oil	[M+] 442.37	MS (m/z) 442
52	thiophene-2-carbonyl chloride	thiophene-2-carbonyl	77-8	62.95, 6.16, 12.23	62.87, 6.25, 12.35
53	isobutyryl chloride	isobutyryl	oil	[M+] 303.40	MS (m/z) 303
54	tetrahydro-furfuryl chloride	tetrahydro furfuryl	oil	[M+] 317.43	MS (m/z) 318
55	benzoyl chloride	benzoyl	72-4	[M+] 337.42	MS (m/z) 338

Ex. #	electrophile	R^2	Mp°C	Mass Spectra or Analysis (Calcd) %C, %H, %N	Mass Spectra/Analysis (found) %C, %H, %N
56	isonicotinoyl chloride	isonicotinoyl	oil	[M+] 338.41	MS (m/z) 339
57	nicotinoyl chloride	nicotinoyl	103-5	[M+] 338.41	MS (m/z) 339
58	2-bromoethylmethyl ether	2-methoxy ethyl	oil	[M+] 291.39	MS (m/z) 292
59	3-(bromomethyl) benzonitrile	3-cyano benzyl	oil	72.39, 6.94, 16.08	72.19, 6.98, 15.75
60	methyl chloro formate	methoxy carbonyl	oil	61.84, 7.26, 14.42	61.34, 7.47, 14.23
61	2-(bromomethyl) benzonitrile	2-cyano benzyl	oil	72.3, 6.9, 16.1	72.5, 7.2, 15.3
62	4-(bromomethyl benzonitrile	4-cyano benzyl	oil	72.3, 6.9, 16.1	70.6, 6.9, 15.5
63	3-bromopropionitrile	2-cyanoethyl	oil	67.09, 7.74, 19.56	66.82, 7.55, 18.92
64	3-bromo-2-butanone	2-butan-3-onyl	59-61	67.3, 8.31, 13.85	67.1, 8.21, 13.50
65	morpholine-4-carbonyl chloride	morpholine-4-carbonyl	153-4	[M+] 346.43	MS (m/z) 347
66	ethylchloro formate	ethoxy carbonyl	oil	[M+] 306.38	MS (m/z) 306
67	2-(2-bromoethyl)-1,3-dioxolane	2-(1,3-dioxolan-2-yl) ethyl	oil	[M+] 333.43	MS (m/z) 334
68	2-(chloro methyl) tetrahydropyran	tetrahydropyran-2-yl methyl	oil	[M+] 331.46	MS (m/z) 332

Example 69

6-(2-Chlorothiophen-5-yl) methyl-3-ethyl-1-(4-fluorophenyl)-7-oxo-4-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-C]pyridine

Reaction of 3-ethyl-1-(4-fluorophenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo [3,4-c]pyridine with 2-chloro-5-(chloromethyl)thiophene, analogous to the procedure of Example 19, affords the title compound. MS (m/z) 390.

Example 70

3-Ethyl-1-(4-fluorophenyl)-7-oxo-6-(thiophen-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

Reaction of 3-ethyl-1-(4-fluorophenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine with 2-chloromethyl thiophene, analogous to the procedure of Example 19, affords the title compound. mp 106-7°C; MS (m/z) 356.

Example 71

1-Cyclopentyl-3-ethyl-6-(2-hydroxy-5-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A solution of 1-cyclopentyl-3-ethyl-6-(2-methoxy-5-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (0.32 grams, 0.91 mmoles) in a 30% solution of HBr in acetic acid (10 ml) is stirred at 95°C. After 24 hours the mixture is concentrated under reduced pressure; dissolved in ethylacetate; washed with saturated sodium bicarbonate and brine; dried over magnesium sulfate and concentrated under reduced pressure. Recrystallization from isopropylether gives 0.15 grams of the title compound. MP 181-2; MS (m/z) 340; Analysis calcd. for $C_{20}H_{25}N_3O_2$: C(70.77), H(7.42), N(12.38). Found C(71.03), H(7.49) N(12.60).

Example 72-78

Reaction of the requisite methoxyphenyl substituted 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine with 30% HBr in glacial acetic acid, analogous to the procedure of Example 71, affords the following compounds of formula IX.

Ex.#	R^1	R^2	R^3	Mp°C	Mass Spectra/ Analysis (Calcd.) %C, %H, %N	Mass Spectra/ Analysis (formed) %C, %H, %N
72	ethyl	2-hydroxy-phenyl	cyclo-pentyl	164-5	[M+]325.41	MS (m/z)326
73	ethyl	3-hydroxy-phenyl	cyclo-hexyl	178-9	[M+]339.44	MS (m/z) 340

Ex.#	R^1	R^2	R^3	Mp°C	Mass Spectra/ Analysis (Calcd.) %C, %H, %N	Mass Spectra/ Analysis (formed) %C, %H, %N
74	ethyl	4-hydroxy-phenyl	cyclo-pentyl	228-9	70.13, 7.12, 12.91	69.02, 7.05, 12.79
75	ethyl	5-chloro-2-hydroxy-phenyl	cyclo-pentyl	124-5	63.41, 6.16, 11.68	63.60, 6.24, 11.56
76	ethyl	5-chloro-2-hydroxy-phenyl	4-fluoro-phenyl	173-4	62.26, 4.44, 10.89	62.41, 4.61, 10.86
77	ethyl	3-hydroxy-phenyl	cyclo-pentyl	161-2	70.13, 7.12, 12.91	70.18, 7.25, 12.86
78	ethyl	3-hydroxy-benzyl	cyclo-pentyl	134-9	[M+]339.44	MS (m/z) 340

Example 79

6-Acetonyl-1-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A solution of 1-cyclopentyl-3-ethyl-6-methallyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (0.12 grams, 0.41 mmoles) indioxane (25 ml) and water (60 ml) is treated with potassium carbonate (0.035 grams) followed by 33m) of a solution of $NaIO_4$ (2.1g) and $KmnO_4$ (0.026 grams) in water (100 ml). After 1 hour the mixture is extracted with ether. The combined ether layers are washed with brine; dried over sodium sulfate and concentrated under reduced pressure. Chromatography on a silica gel column using 1:3 ethylacetate/hexane as eluent gives 0.042 grams of the title compound as a colorless oil. MS (m/z) 290.

Example 80

1-cyclopentyl-3-ethyl-6-(2-hydroxypropyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A solution of 6-acetonyl-1-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (30 m grams, 0.10 mmoles) in anhydrous methanol (2ml) at 0°C is treated with sodium borohydride (38 mgrams). After 15 minutes aqueous saturated ammonium chloride is added and the mixture is extracted with ether. The combined ether layers are washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Chromatography on a silica gel column using 1:2 ethyl

acetate/hexane as eluent gives 20 mgrams of the title compound as a colorless oil. MS (m/z) 292.

Example 81

6-(Aceton-1-yloxime)-1-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A solution of 6-Acetonyl-1-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (o.15 grams0 in anhydrous pyridine (5ml) is treated with hydroxylamine hydrochloride (0.040 grams) at ambient temperature. After 20 hours the mixture is concentrated under reduced pressure and then suspended in ethyl acetate. The suspension is washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization from isopropyl ether gives 0.10 grams of the title compound as a white solid. MP 147-9°C; MS (m/z) 305; Analysis calcd. for $C_{16}H_{24}N_4O_2$; C(63.13), H(7.94, N(18.41). Found C(62.80), H (8.20), N (18.55).

Example 82

6-(O-Aminocarbonyloximeacetonyl)-1-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A solution of 6-(oximeacetonyl)-1-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (0.10 grams) in THF (5ml) at 0°C is treated with chlorosulfonly isocyanate (70 mgrams). After stirring for 1 hours at 25°C the mixture is concentrated under reduced pressure, dissolved in ethyl acetate; washed with water and brine; dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography on a silica gel column eluting with 1:3 ethylacetate/hexane gives the title compound as a pale yellow oil. MS (m/z) 348.

Examples 83-86

Reaction of 1-cyclopentyl-3-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine with sodium hydride in DMF followed by the addition of the requisite electrophile, analogous to the procedure of Example 19, affords the following compounds of formula X where R^1=ethyl and R^3=cyclopentyl.

Ex. #	Electrophile	R^2	MP°C	Mass Spectra or Analysis (calcd.) %C, %H, %N	Mass Spectra or Analysis (found) %C, %H, %N
83	isopropyl-sulfonyl-chloride	isopropyl-sulfonyl	108-113	59.05, 8.37, 112.91	58.79, 8.38, 12.51

84	thiophene-2-carbonyl-chloride	thiophene-2-carbonyl	oil	65.62, 7.04, 12.75	62.60, 6.74, 11.84
85	dimethyl-carbamyl	dimethyl-carbamyl	oil	[M⁺] 290.41	MS (m/z) 291
86	2-chloro-5-(chloro-methyl) thiophene	2-chloro-thiophen-5-yl methyl	oil	[M⁺] 349.93	MS (m/z) 350

Preparation 1

4-Isobutyryl-3-methoxy-1-phenyl-2-oxo-1,2,5,6-tetrahydropyridine

A stirred solution of freshly distilled diisopropylamine (0.16 ml, 2.21 mmole) in anhydrous tetrahydrofuran (4 ml) was cooled to 0°C and treated with 2.5 M n-butyl lithium (0.85 ml, 2.11 mmole). After 15 minutes the mixture was cooled to -78°C and a pre-cooled solution of 4-propionyl-3-methoxy-1-phenyl-2-oxo-1,2,5,6-tetrahydropyridine (0.52 grams, 2.0 mmole) in tetrahydrofuran (4 ml) was added dropwise via cannula. After approximately 20 minutes methyl iodide (0.20 ml, 3.0 mmole) was added to the bright orange-red solution and the mixture was allowed to come to room temperature over 2.5 hours. The reaction mixture is poured into saturated aqueous ammonium chloride and the organic layer is washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column using 1:4 ethyl acetate/hexane as eluent gives 0.12 grams of the title compound as a yellow oil and 0.1 grams of recovered starting material. ^{1}H NMR (250 MHz, $CDCl_3$) 1.15 (d, 6H), 2.72 (t, 2H), 3.47 (heptet, 1H), 3.82 (t, 2H), 3.97 (s, 3H), 7.21-7.45 (m, 5H); MS m/z [M⁺] 274.

Preparations 2-3

Reaction of the appropriate 3-methoxy-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine with lithium diisopropylamine and methyl iodide, analogous to the procedure of preparation 1, affords the following compounds of formula VII.

Prep#	R^2	m.p. °C	M.W.	Mass Spectra [M⁺]
2	4-methoxyphenyl	oil	303.36	304
3	3-methoxyphenyl	oil	303.36	304

Preparation 4

3-Methoxy-1-(4-methylphenyl)-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine

A solution of 3-hydroxy-1-(4-methylphenyl)-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine (5.9 grams, 23 mmole) and 3-methyl-1-p-tolyltriazine (5.1 grams, 34 mmole) in 1,2-dichloroethane was heated to reflux for 45 minutes. The mixture was allowed to cool to room temperature and was poured into water and acidified with 6N hydrochloric acid. The aqueous layer was extracted 3 times with methylene chloride, and the combined organics are washed with 1N hydrochloric acid followed by water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting quantitative brown oil was clean by thin layer chromatography and ^{1}H NMR and was used without purification. ^{1}H NMR (300 MHz, $CDCl_3$) 1.12 (t,J = 7.2 Hz, 3H), 2.34 (s, 3H), 2.71 (t,J = 6.7 Hz, 2H), 2.93 (q,J = 7.2 Hz, 2H), 3.77 (t,J = 6.8 Hz, 2H), 3.94 (s, 3H), 7.20 (s, 4H); MS [M^+] 273.

Preparations 5-14

Reaction of the appropriate 3-hydroxy-1-aryl-2-oxo-4-alkanoyl-1,2,5,6-tetrahydropyridine with 3-methyl-1-p-tolyltriazine, analogous to the procedure of Preparation 4, affords the following compounds of formula VI.

Prep#	R^1	R^2	m.p. °C	M.W.	Mass Spectra [M^+]
5	ethyl	phenyl	oil	259.31	260
6	methyl	4-methoxyphenyl	oil	275.30	275
7	ethyl	4-methoxyphenyl	81-82	289.33	289
8	n-propyl	4-methoxyphenyl	oil	303.36	303
9	ethyl	3-methoxyphenyl	59-60	289.33	289, 290
10	ethyl	2-methoxyphenyl	oil	289.33	289
11	ethyl	3,4-dimethoxyphenyl	oil	319.26	319
12	ethyl	3-cyclopentoxy-4-methoxyphenyl	oil	373.45	373
13	ethyl	3-methylphenyl	oil	273.33	273
14	ethyl	3-trifluoromethylphenyl	oil	327.30	327

Preparation 15

3-Hydroxy-1-(3-methylphenyl)-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine

To a stirred suspension of magnesium turnings (1.9 grams, 79 mmole) in 30 ml of anhydrous ether was added dropwise bromoethane (5.9 ml, 79 mmole). A mild reflux was initiated after approximately 1 ml was added. After all of the magnesium was consumed, the reaction mixture was cooled to 0°C and N-(3-methylphenyl)-2-pyrrolidone (8.7 grams, 50 mmole) was added at once. After warming to room temperature and stirring for 2 hours the reaction mixture was poured over ice and extracted with ethyl acetate. The combined organics are washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 8.8 grams of a white solid.

The above solid is dispersed in a mixture of 40 ml benzene and 86 ml 1N sodium hydroxide, and with vigorous mechanical stirring ethyl oxalyl chloride (7.2 ml, 64 mmole) was added. After stirring at reflux over 1.5 hours the layers are separated and the aqueous layer was extracted with ethyl acetate. The combined organics are washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give an amber oil. GCMS [M^+] 305.

The above intermediate was dissolved in 20 ml anhydrous ethanol and treated with a solution of sodium methoxide in methanol (prepared from the careful addition of sodium (1.0 grams) to 10 ml anhydrous methanol). After being stirred at reflux over 1.5 hours, the mixture was concentrated under reduced pressure and 100 ml of water was added. The mixture was acidified to pH 3 with 6N hydrochloric acid and the dull yellow precipitate was filtered and washed with water. Recrystallization from 75 ml isopropyl ether affords 6.8 grams of pale yellow crystals. M.P. 115-116°; ^{1}H NMR (300 MHz, $CDCl_3$) 1.16 (t,J = 7.2 Hz, 3H), 2.37 (s, 3H), 2.74-2.82 (m, 4H), 3.85 (t,J = 6.8 Hz, 2H), 7.08-7.14 (m, 3H), 7.30 (t,J = 7.7 Hz, 1H); MS m/z [M^+] 259.

Preparations 16-29

Reaction of the appropriate 2-pyrrolidinone with the requisite alkylmagnesium bromide, followed by treatment with ethyl oxalyl chloride and base, analogous to that reported in Preparation 15, affords the following compounds of formula VI.

Prep#	R^1	R^2	m.p. °C	M.W.	Mass Spectra [M^+]

16	methyl	phenyl	oil	231.25	231
17	ethyl	phenyl	140-142	245.28	245
18	ethyl	4-fluorophenyl	133-135	263.27	263
19	methyl	4-methoxyphenyl	oil	261.28	262
20	ethyl	4-methoxyphenyl	121-122	275.30	276
21	n-propyl	4-methoxyphenyl	125-126	289.33	289
22	ethyl	3-methoxyphenyl	129-130	275.30	275
23	ethyl	2-methoxyphenyl	119-120	275.30	275
24	ethyl	4-methylphenyl	110-112	259.30	260
25	ethyl	2-methylphenyl	oil	259.30	259
26	ethyl	3-trifluoromethylphenyl	117-118	313.28	313
27	ethyl	2-trifluoromethylphenyl	oil	313.28	313
28	ethyl	3,4-dimethoxyphenyl	179-180	305.33	306
29	ethyl	3-cyclopentoxy-4-methoxyphenyl	133-134	359.42	360

Preparation 30

N-(2-Methoxyphenyl)-2-pyrrolidone

A mixture of 2-pyrrolidone (15.0 grams, 176 mmole), 2-iodoanisole (7.6 ml, 59 mmole), copper powder (7.5 grams, 117 mmole) and potassium carbonate (8.1 grams, 59 mmole) are stirred under nitrogen at 150°C. After 18 hours, the reaction mixture was filtered through a 6x15 cm pad of silica gel eluting with 1:1 ethyl acetate/hexane to give a pale yellow oil. The unreacted reagents are removed by vacuum distillation (0.6 mm, 80-100°C) leaving 9.2 grams of the title compound as a honey-like oil. ^{1}H NMR (300 MHz, $CDCl_3$) 2.20 (pentet, 2H), 2.55 (t, 2H), 3.75 (t, 2H), 3.82 (s, 3H), 6.93-7.02 (m, 2H), 7.25-7.30 (m, 2H); MS m/z [M^+] 191.

Preparations 31-39

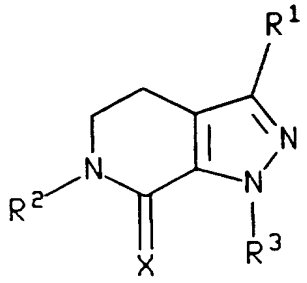
Reactions of the appropriate iodo- or bromobenzene with 2-pyrrolidinone, analogous to that reported in Preparation 30, affords the following compounds of formula V.

Prep#	R	M.W.	Mass Spectra [M^+]

31	4-methoxyphenyl	191.22	191
32	3-methoxyphenyl	191.22	191
33	3-methylphenyl	175.23	175
34	4-methylphenyl	175.23	175
35	2-methylphenyl	175.23	175
36	3-trifluoromethylphenyl	229.20	229
37	2-trifluoromethylphenyl	229.20	229
38	3,4-dimethoxyphenyl	221.26	221
39	3-cyclopentoxy-4-methoxyphenyl	275.35	275

CLAIMS

1. A compound of the formula



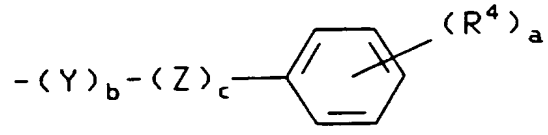
I

and pharmaceutically acceptable salts thereof;

wherein R^1 is hydrogen, (C^1-C^3)alkyl, (C^2-C^3)alkenyl, (C^3-C^5)cycloalkyl or methylene (C^3-C^5)cycloalkyl wherein each alkyl or alkenyl group may be optionally substituted with up to two (C^1-C^2)alkyl or trifluoromethyl groups or up to three halogens;

X is oxygen or two hydrogen atoms;

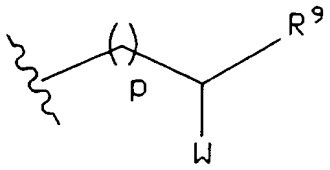
R^2 and R^3 are each independently selected from the group consisting of hydrogen; (C^1-C^{14})alkyl optionally substituted with halogen or cyano; (C^1-C^{14})alkyl sulfonyl; (C^1-C^{14})alkoxy; naphthalyl; (C^2-C^7)alkenyl; (C^3-C^7)cycloalkyl; (C^1-C^4)alkyl(C^3-C^7)cycloalkyl; (C^3-C^7)cycloalkyl(C^1-C^4)alkyl; (C^4-C^7)heterocyclic group containing oxygen; sulphur; SO_2 or NR^5 wherein R^5 is hydrogen or (C^1-C^4)alkyl; (C^4-C^7)heterocycloalkyl-$(W)_d$ wherein the (C^4-C^7)heterocycloalkyl group contains one or more oxygen; sulphur; SO_2 or NR^5 groups wherein R^5 is hydrogen or (C^1-C^4)alkyl optionally substituted with halogen or (C^1-C^4)alkyl, d is 0 or 1 and W is (C^1-C^4)alkyl, CO or sulfonyl; $CONR^{10}R^{11}$ wherein R^{10} and R^{11} are each independently hydrogen or (C^1-C^4)alkyl; (C^1-C^5)alkyl carbonyl; (C^1-C^5)alkoxy carbonyl; (C^1-C^5)alkyl carbonyl (C^1-C^5)alkyl; (C^1-C^5)alkoxy carbonyl (C^1-C^5)alkyl; (C^1-C^5)alkoxy(C^1-C^5)alkyl; $R^{12}R^{13}N$(C^1-C^5)alkyl wherein R^{12} and R^{13} are each independently hydrogen or (C^1-C^5)alkyl; or a group of the formula



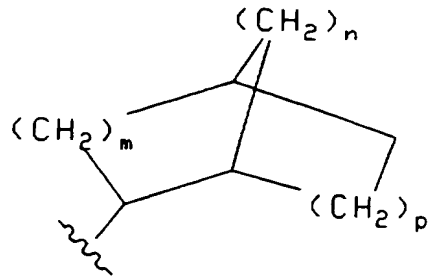
II

wherein a is an integer from 0 to 5; b and c is O or 1; R^4 is independently selected from hydrogen, hydroxy, (C^1-C^5)alkyl, (C^2-C^5)alkenyl, (C^1-C^5)alkoxy, (C^3-C^6)cycloalkoxy,

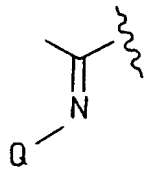
halogen, trifluoromethyl, CO_2R^6, $CONR^6R^7$, NR^6R^7, CONHOH, CN, NO_2 or $SO_2NR^6R^7$ wherein R^6 and R^7 are each independently hydrogen or (C^1-C^4)alkyl; wherein Y is (C^1-C^4)alkyl, (C^2-C^5)alkylene or (C^2-C^6)alkenyl optionally substituted with up to two (C^1-C^7)alkyl or (C^3-C^7)cycloalkyl groups; and Z is oxygen, sulphur, CO, SO_2 or NR^8 wherein R^8 is hydrogen or (C^1-C^4)alkyl; or a group of the formula



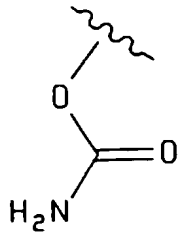
wherein p is an integer from 1 to 3, W is hydroxy, R^9 is (C^1-C^3)alkyl; wherein each said alkyl, alkenyl, cycloalkyl, alkoxyalkyl or heterocyclic group may be optionally substituted with one to fourteen, preferably one to five, of the group consisting of (C^1-C^2)alkyl, trifluoromethyl or halogen; or the group of the formula



wherein m, n and p are 1 or 2; or a group of the formula

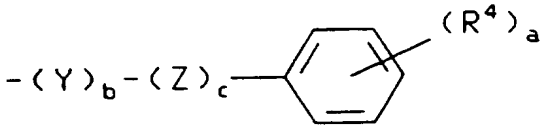


wherein Q is hydroxy or a group of the formula



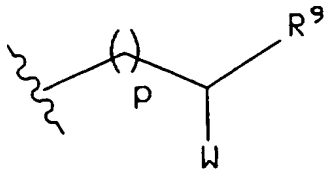
with the proviso that when R^1 is ethyl and R^2 is 4-methylphenyl, R^3 cannot be hydrogen, methyl, phenyl, 4-fluorophenyl or 2-pyridyl and with the proviso that when R^2 is 4-methylphenyl and R^3 is 4-fluorophenyl, R^1 cannot be phenyl, methyl or n-propyl and with the proviso that when R^1 is ethyl and R^2 is phenyl, R^3 cannot be 4-chlorophenyl, 4-fluorophenyl or 4-methylphenyl, with the proviso that when R^1 is ethyl and R^2 is 4-methoxyphenyl, R^3 cannot be 4-fluorophenyl and with the proviso that when W is CO or sulfonyl, d is 1;

with the proviso that R^2 and R^3 cannot both be independently selected from the group consisting of hydrogen, $(C^1\text{-}C^{14})$alkyl, $(C^1\text{-}C^{14})$alkoxy, $(C^2\text{-}C^7)$alkenyl, $(C^4\text{-}C^7)$heterocyclic group containing oxygen, sulphur, SO_2 or NR^5 wherein R^5 is hydrogen or $(C^1\text{-}C^4)$alkyl, or a group of the formula



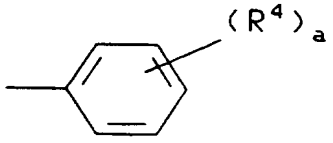
II

wherein a is an integer from 1 to 5; b and c is O or 1; R^4 is hydrogen, hydroxy, $(C^1\text{-}C^5)$alkyl, $(C^2\text{-}C^5)$alkenyl, $(C^1\text{-}C^5)$alkoxy, $(C^3\text{-}C^6)$cycloalkoxy, halogen, trifluoromethyl, CO_2R^6, $CONR^6R^7$, NR^6R^7, NO_2 or $SO_2NR^6R^7$ wherein R^6 and R^7 are each independently hydrogen or $(C^1\text{-}C^4)$alkyl; wherein Z is oxygen, sulphur, SO_2 or NR^8 wherein R^8 is hydrogen or $(C^1\text{-}C^4)$alkyl; and Y is $(C^1\text{-}C^5)$alkylene or $(C^2\text{-}C^6)$alkenyl optionally substituted with up to two $(C^1\text{-}C^7)$alkyl or $(C^3\text{-}C^7)$cycloalkyl groups; or a group of the formula



wherein p is an integer from 1 to 3, W is oxo or hydroxy, R^9 is (C^1-C^3)alkyl; wherein each said alkyl, alkenyl, cycloalkyl, alkoxyalkyl or heterocyclic group may be optionally substituted with one to fourteen, preferably one to five, of the group consisting of (C^1-C^2)alkyl, trifluoromethyl or halogen.

2. A compound according to claim 1 wherein R^1 is (C^1-C^3)alkyl and R^3 is (C^3-C^7)cycloalkyl, (C^4-C^7)heterocyclic group containing SO_2 or a group of the formula



III

wherein a is an integer from 1 to 5 and R^4 is independently selected from hydrogen, hydroxy, (C^1-C^5)alkyl, (C^1-C^5)alkoxy or halogen.

3. A compound according to claim 1 wherein R^1 is ethyl or isopropyl; R^2 is phenyl,2-methylphenyl,3-methylphenyl,2-methoxyphenyl,3-methoxyphenyl,2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, cyclopropylmethyl, benzyl, isobutyl, isobutenyl, 2-ethylphenyl, naphthalenyl, 2-chlorophenyl, 3-methylbutyl, dimethylcarbamyl, 1-methylbenzyl, isopropyl, 1-picolyl, 2-picolyl, 3-picolyl, 2-methyl-5-chlorophenyl, 2-chlorothiophen-5-ylmethyl, 2-hydroxy-5-methylphenyl, 3,5-dimethyl-isoxazol-4-ylmethyl, 3-chlorobenzyl, thiophen-2-ylmethyl, 2-hydroxy-5-chlorophenyl, thiophene-2-carbonyl, tetrahydrofurfuryl, 3-cyanobenzyl, morpholine-4-carbonyl, isopropylsulfonyl, 4-methoxyphenylsulfonyl or 3-trifluoromethylphenyl, and R^3 is cyclobutyl, cyclopentyl, cyclohexyl, 3-sulfolanyl, 4-fluorophenyl or 3,4-dichlorophenyl.

4. A pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) and for the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising a pharmaceutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

5. A method for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) comprising administering to a patient an effective amount of a compound according to claim 1.

6. A method of treating or preventing a condition selected from the group consisting of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis,

allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising administering to a patient an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

Intern[illegible]plicaton No
PCT/I[illegible]/00847

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/435 //(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL AND PHARMACEUTICAL BULLETIN., vol.24, no.8, 1976, TOKYO JP pages 1870 - 1878 T. KAMETANI ET AL 'Studies on the syntheses of heterocyclic compounds. DCLXIII. The reaction of pyridone derivatives with diazoalkane' see page 1871; example VII	1
X	FR,A,1 463 883 (CIBA) 30 January 1966 see claim 49	1
P,X	WO,A,95 01980 (PFIZER) 19 January 1995 see claims 1,5,7	1,4

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
27 December 1995	04.01.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Voyiazoglou, D

Form PCT ISA 210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

tional application No.
PCT/IB 95/00847

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 5 and 6 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter. [illegible]lication No
PCT/IB[illegible]/00847

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A-1463883	10-03-67	BE-A-	669298	07-03-66
		FR-M-	5155	12-06-67
		FR-M-	4903	
		NL-A-	6511645	09-03-66
		US-A-	3340269	05-09-67
		US-A-	3365459	23-01-68
		OA-A-	1821	14-01-70
WO-A-9501980	19-01-95	AU-B-	6805794	06-02-95
		FI-A-	943208	07-01-95